U.S. EPA BOARD OF SCIENTIFIC COUNSELORS
Human Health Subcommittee Meeting Summary

Environmental Protection Agency
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Welcome and Opening Remarks

Dr. James Klaunig, Chair, Human Health Subcommittee

Dr. James Klaunig welcomed participants to the meeting of the U.S. Environmental Protection Agency (EPA) Board of Scientific Counselors (BOSC) Human Health Subcommittee and asked the panelists to introduce themselves:

- Dr. Elaine Symanski, from the University of Texas School of Public Health
- Dr. Joseph Landolph, from the University of Southern California's Keck School of Medicine
- Dr. Michael Jayjock, from the LifeLine Group
- Dr. James Klaunig, from the Indiana University School of Medicine
- Dr. James Clark, from the Exxon Mobil Research and Engineering Company
- Dr. Timothy Buckley, from the Johns Hopkins University School of Public Health
- Mr. Harvey Clewell, from the Chemical Industry Institute of Toxicology Centers for Health Research.

Dr. William Farland was unable to attend the meeting, and Dr. Donald Mattison attended the second and third days of the meeting.

Three panelists made disclosures involving potential conflicts of interest. Dr. Jayjock was peripherally involved with the preparation of a white paper for the Office of Research and Development (ORD). In addition, he has made public statements about the need for exposure research. Mr. Clewell has done work for ORD in the past. Dr. Landolph made some public statements 3 or 4 years ago on chromium toxicology and carcinogenesis and does some occasional part-time consulting for litigation support.

A full list of the meeting participants can be found at the end of this summary, and the meeting agenda appears in the appendix.

DFO Welcome and Charge
Ms. Virginia Houk, DFO/EPA, Human Health Subcommittee

Ms. Virginia Houk, the Designated Federal Officer (DFO) for the Human Health Subcommittee, thanked the co-chairs, the subcommittee members, and the public for their attendance at the meeting. She reviewed the administrative procedures and Federal Advisory Committee Act (FACA) rules and described the objective of the subcommittee and its charge.

As a federal advisory committee, the BOSC provides independent, scientific peer review and advice to EPA's ORD. The Human Health Subcommittee was established by the BOSC Executive Committee to review ORD's Human Health Research Program (HHRP). The subcommittee has been asked to respond to charge questions and to provide a report to the BOSC Executive Committee. The Executive Committee will review the subcommittee's report, revise it as necessary, and submit it to ORD. Whereas the role of the BOSC is to provide advice and recommendations to ORD, the rights of decision-making and program implementation remain with EPA.

This first face-to-face meeting of the subcommittee was preceded by two conference calls in the past 3 weeks, and a third conference call will be held within the next month. Additional meetings can be scheduled if necessary. The subcommittee is expected to provide an oral presentation on Wednesday to share its draft findings. A draft final report will be presented to the BOSC.

The DFO serves as the liaison between the subcommittee and EPA and is responsible for ensuring that the subcommittee and its meetings comply with FACA. Ms. Houk explained some relevant FACA rules and procedures:

- All meetings involving substantive issues, whether in person, via telephone, or by e-mail, are open to the public. This rule applies to all group communications that include at least one-half of the subcommittee members. Issues that are solely administrative or preparatory in nature are exempt from this requirement.
- A *Federal Register* notice must announce all meetings and calls 15 calendar days in advance.
- The DFO must approve the agenda and attend all meetings and calls.
- Meeting minutes must be certified by the Chair within 90 days of the meeting.
- All advisory committee documents must be made available to the public.

The DFO has worked with EPA officials to ensure that all appropriate ethics regulations are satisfied. Each subcommittee member has filed a standard government financial disclosure report. These reports are reviewed by the Deputy Ethics Officer of ORD's Office of Science Policy and the DFO in consultation with the Office of General Counsel to ensure that all ethics requirements are met. In addition, the subcommittee members have completed their ethics training.

Ms. Houk concluded her presentation by describing the process for agenda development and public comment and covering other housekeeping issues.

ORD's Welcome and Introduction to the Review of ORD's Human Health Research Program

Dr. Lawrence Reiter, Director, National Health and Environmental Effects Research Laboratory (NHEERL)/EPA

Because Dr. Farland was unable to attend the meeting, Dr. Lawrence Reiter welcomed the participants on behalf of ORD and thanked the panel members for their work on the review of the research program. His presentation included background information on the program reviews, ORD's expectations regarding the review, and an overview of the agenda.

ORD's commitment to an external review of its research programs has been reinforced by a number of diverse groups, including the National Academy of Sciences (NAS) and the Office of Management and Budget (OMB). ORD uses external review to develop its strategic plans, multi-year plans (MYPs), and Laboratory implementation plans. NAS has recommended independent expert review for evaluation of federal research programs. OMB highlights the value of recommendations from independent expert review in guidance to federal agencies. ORD is strongly committed to independent expert review for objective evaluation of research at the program level. ORD asked the BOSC to participate in the review of its scientific programs and to examine issues related to both implementation and results.

Recommendations from the BOSC program reviews will provide guidance to ORD to help implement and strengthen the research program, verify when clients have applied research to strengthen environmental decisions, make decisions about research investments and disinvestments over the next 5 years, and prepare EPA's performance and accountability reports to Congress under the Government Performance and Results Act. The evaluation criteria for the research programs involve relevance, quality, and accountability. These evaluation criteria coincide with the investment criteria developed by OMB and the Office of Science and Technology Policy (OSTP), which ask programs to focus on the three critical areas of relevance, quality, and performance. In addition, OMB and OSTP encourage research managers to characterize scientific leadership.

In the area of relevance of the HHRP, the fundamental question is whether the research is serving the Agency's needs. Is there an overall conceptual framework with clear goals and priorities? Is the program based on Agency priorities and does it include input from potential users of the research outputs? Is the core research relevant to problem-driven areas of high priority to the Agency? Does the program leverage its efforts with federal and other laboratories to study high-impact environmental questions?

In the area of quality of the HHRP, the fundamental question is whether ORD is "not only doing the right science but also doing the science right." Are the performance and outcomes from the program reviewed prospectively and retrospectively by an external peer-review mechanism? Are funds allocated using a merit-based process?

In the area of performance of the HHRP, the fundamental question is whether the program is productive. Are outcomes tracked using an MYP having annual performance measures and

milestones? Does the research contribute to the completion of the long-term goals (LTGs) of the MYP?

In the area of the scientific leadership of the HHRP, the questions involve whether the scientists in the program are generating an appropriate level of peer-reviewed publications and are recognized by the scientific community. Do the scientists serve as advisors to other research organizations, as elected officials to scientific societies, and on editorial boards of scientific peer-review journals? Are they involved in teaching or training?

The BOSC subcommittee program review is structured according to four themes that overlay with the four LTGs in the MYP: (1) mechanistic data, (2) aggregate/cumulative risk, (3) susceptible subpopulations, and (4) public health outcomes. The presentations are intended to provide the context for the LTGs. Each overview will be followed by a poster session, in which the principal investigators (PIs) will provide more indepth descriptions of the research. The posters, which represent an aggregate body of information, will be presented by ORD scientists from all of the Laboratories and Centers as well as Program Office scientists who are collaborators and clients. Following the poster sessions, the panel members will meet collectively with the PIs for discussions to provide additional information, address questions, or clarify issues. The final day of the meeting will include Program Office, Regional Office, and extramural research presentations.

Overview of the Human Health Research Program
Dr. Larry Cupitt, National Exposure Research Laboratory (NERL)/ORD/EPA

Dr. Larry Cupitt began his presentation with an explanation of what ORD is asking the panelists to review, namely, the relevance, quality, performance, and scientific leadership in the core HHRP. The core research has applicability across a broad variety of programs. The panelists are asked to evaluate the program to date and provide guidance for future directions and plans as ORD prepares for the Performance Assessment Rating Tool (PART) review.

The concept of core research as applied to the HHRP derives from the National Research Council's (NRC's) report from the Committee on Research Opportunities and Priorities for EPA (ROPE). According to the ROPE report, EPA should focus on two types of research: problem-driven research and core research. Core research projects are based on broad applicability, relevance to the Agency, and scientific merit. They support the Agency's work in air toxics, mercury, drinking water, safe food, and so on. Dr. Cupitt described human health research in the context of the Agency's goals as formulated in EPA's Strategic Plan and ORD's Strategic Plan. The Human Health Research Strategy defined a risk assessment paradigm and stated key issues in four long-term research themes. The MYP was meant to be revised biennially, and the Laboratory and Center implementation plans are revised annually based on the budget and the determination of priorities.

Dr. Cupitt described the program design and evaluation in terms of a logic model. The paradigm attempts to link a source to a final health outcome and understand the way in which that transition occurs. Risk assessment is critical in deciding whether to take regulatory action against an environmental hazard and determining the actions that are most effective to protect human

health. Risk assessment also is critical in evaluating the ultimate effectiveness of the actions taken. ORD is unique because its research covers all of the components in the source-exposure-dose-effects continuum of the paradigm.

In the process of implementing research priorities, research staff and managers must balance executive-level guidance and strategies; appropriated resource levels; advice from Program Offices, Regions, and stakeholders; technical peer review; and progress to date under the MYP. ORD attempts to match the highest priority needs with the available resources and skills, integrating Science To Achieve Results (STAR) and intramural research. ORD then develops the annual Laboratory and Division implementation plans and provides feedback to amend the MYP. Periodically, ORD's research staff members meet to reassess the priorities and suggest revisions to the MYP. The topic areas described in the LTG presentations represent current refinements to the MYP.

ORD uses the science planning to affect its budget contingencies. It involves its staff, Program Office staff, and regional representatives in evaluating research areas within the human health plan for their importance and contribution to the overall science effort. The areas then are ranked, and the recommendations are submitted to the Executive Committee, which weighs the needs and priorities against the total research programs. The major mandates for research to improve human health risk assessment at EPA come from congressional legislation, scientific panels, and scientific relationships, which include the use of mechanistic data in risk assessments, the reduction in uncertainties in aggregate and cumulative risk, the protection of susceptible subpopulations, and the evaluation of the effectiveness of risk management decisions (public health outcomes).

The key questions involved in the LTGs are as follows: What are the important issues for the LTGs? What are the key scientific questions about the issues that must be understood because of their impact on risk assessment? How do we measure, model, and/or predict the key attributes? How do we incorporate our knowledge to improve risk assessment and risk management? Dr. Cupitt asked the panel members to evaluate the following aspects of each of the LTGs: (1) broad applicability in selected research areas, (2) progress to meet the LTG, (3) relevance and successful application to problem-driven research efforts, and (4) quality and impact of scientific effort. The next steps for ORD scientists will be to revise the human health MYP on the basis of the panel's advice and prepare for the PART evaluation by OMB.

Dr. Clark posed a question regarding the idea of scientific leadership. How do EPA scientists set the agenda, that is, how do they determine the questions to be asked based on the data they collect? Dr. Cupitt stated that ORD used the research coordination teams (RCTs) as well as scientists from across the Agency to create the MYP. The strong working relationship enabled ORD to examine the diverse program holistically. Dr. Reiter stated that the MYP is "where the rubber hits the road." The development of the context of the LTGs is a top-down process in that it relies on external sources, but the creation of the research program entails bottom-up participation. The MYPs are developed by writing teams, and the Laboratories and Centers develop the implementation plans.

Mr. Clewell expressed some confusion about how the National Center for Computational Toxicology (NCCT) will affect the research. Dr. Robert Kavlock stated that a poster will address this concern, and a BOSC subcommittee meeting at the end of April will answer the question of how the NCCT will feed back into the program.

Dr. Landolph asked about the ROPE report and was told that it is available on the NRC Web Site and that a copy would be obtained for him. Dr. Cupitt stated that the major point made in the ROPE report was the need for a balance between core and problem-driven research. Dr. Reiter added that the report was issued in 1997 and afforded EPA an opportunity to formalize a core research program.

Dr. Buckley asked whether the LTGs, which are at the heart of the HHRP, were defined within the Agency or whether they were defined externally and are being implemented internally. If they were defined by the Agency, what is the process by which they were articulated? Dr. Cupitt stated that ORD agreed with the recommendations set forth in the research strategy. Dr. Buckley asked whether the scientific advisory board or the Agency defined the categories of focus. Dr. Hal Zenick explained that the HHRP was originally project driven. A concerted effort was made in ORD to focus its capabilities on the most critical aspects of risk assessment. This maturing of the program has occurred over the past 7 years. Dr. Clark remarked that leadership within ORD interacted with clients to conduct more efficient risk assessments by making the reduction of uncertainty a high priority. The scientists helped to set the agenda by asking clients for advice about how ORD could improve its performance. Dr. Cupitt added that the core research program is an opportunity to examine the longer term needs. Dr. Clark reiterated ORD's involvement in setting an agenda as a leadership role.

Dr. Buckley referred to the conceptual model of the continuum and asked to what extent the top three boxes on the left-hand side fit into the human health program. Dr. Cupitt responded that ORD can leverage the work in the problem-driven area, for example, to respond to the exposure model. Regarding risk management questions, the source must be understood before effective action can be taken. The human health core research program has been focused largely on the continuum from exposure to dose to early biological effect to altered structure or function to disease.

Dr. Klaunig described the way in which the panel will function over the course of the meeting. Lead writers were assigned to the four LTGs, and a fifth category (testimonials) was devised. Drs. Landolph, Jayjock, Buckley, and Symanski are the lead writers for LTG 1, LTG 2, LTG 3, and LTG 4, respectively. Dr. Mattison and Mr. Clewell will report on the testimonials from clients. Secondary writers and poster reviewers also have been assigned, preliminary writing has begun, and panelists will offer feedback. An overview of the preliminary findings will be presented on Wednesday, and additional writing will be done after the meeting. A third conference call is planned to discuss the final draft document. Dr. Clark added that the panel must be responsive and timely to help ORD in its PART review.

HHRP Long-Term Goal 1 (LTG 1): Use of Mechanistic Data in Risk Assessment

LTG 1: Overview—Use of Mechanistic Data in Risk Assessment

Dr. Julian Preston, NHEERL/ORD/EPA

Dr. Julian Preston presented an overview of LTG 1 to provide a context for the posters associated with this goal. NAS recommended that EPA develop a harmonized risk assessment process for the different disease endpoints and, in addition, use mechanistic data on disease formation in support of risk assessments. Risk assessors and risk managers should use ORD's mechanistic methods and models to decrease uncertainty in risk assessment, which in turn reduces risk to humans exposed to environmental stressors. The examples fall into three categories: (1) research that has clearly had an impact, (2) ongoing research that is beginning to have an impact, and (3) newly initiated research that will have an impact.

The goal is to be able to describe total risk (detriment) to exposed populations using a harmonized risk assessment approach. This approach requires understanding of the key events involved in induction of cancer and noncancer diseases from exposure to environmental chemicals. The human health MYP identifies research projects to meet the short- and medium-range goals, and the research and implementation plans are presented in the abstracts and posters.

The research is designed to identify specific issues underlying each of the following questions: Which modes or mechanisms of action (MOA) are important for understanding the impact of environmental stressors on human health? What are the attributes of the MOA that affect risk assessment? How do we measure, model, and/or predict the key attributes of the MOA that could affect risk assessment? How do we incorporate mechanistic tools into risk assessment?
Dr. Preston described the approach and impact of six ORD research areas represented in the posters (Ah receptor and dioxin, luteinizing hormone disruption, arsenic carcinogenicity, conazoles, oxidative stress, and risk assessment applications of MOA and computational toxicology) corresponding to the key research questions.

Regarding the second key research question and the example of cancer risk at low concentrations of arsenic, Dr. Clark posed a question about how information on this investigation is communicated to potential users to inform them about advances in knowledge. Dr. Preston responded that project leaders maintain interaction through conference calls with the Program Offices. Research scientists are becoming increasingly more involved in the regulatory process. Dr. Clark mentioned from his own experience that a number of investigators would find that interaction burdensome. Dr. Preston responded that when the problem is handled in a positive way, investigators begin to see the value of positive feedback. In addition, the enthusiasm of Division directors enhances the interaction.

Dr. Landolph asked about the seriousness of the problem involving conazoles and the impetus for the problem coming to the Environmental Carcinogenesis Division. Dr. Preston explained that interaction between the Division and one of the Program Offices led to the identification of a critical need in this area.

Dr. Buckley asked Dr. Preston to comment on the interaction between LTG 1 and the other LTGs. Dr. Preston responded that the interaction is natural and common; for example, arsenic has a susceptible population component. He explained that the problem of susceptibility associated with conazoles and children can be viewed as a generic or a specific issue.
Dr. Buckley asked whether the interaction occurs among the scientists or the research planners. Dr. Preston responded that, as an ongoing activity, the interaction would occur among the research scientists, but initially it would occur among the research planners. Dr. Buckley asked whether coauthors on the topic of MOA also might be seen in the susceptibility group.
Dr. Preston's response was that interactions occur and the same coauthors can be seen across the LTGs.

Discussion

After the poster session, Dr. Reiter referred to the NAS ROPE report (page 62) and its recommendations to develop internal mechanisms for continually identifying emerging issues; cooperate closely with other research organizations; compile, publish, and disseminate an annual summary of research; conduct retrospective evaluations of the effectiveness of environmental policy decisions; and make long-term financial and intellectual commitments to research projects. Dr. Reiter commented that ORD has complied with these recommendations.

The panelists engaged in a discussion of LTG 1, lead by Dr. Landolph, who opened the session with remarks about the posters on arsenic, conazoles, and oxidative stress, an area that needs focus on specific substances and diseases. Dr. Landolph called for comments from the panel on each of the six topic areas: (1) Ah receptor mechanism, (2) oxidative stress, (3) luteinizing hormone disruption, (4) missed mode of action, (5) p450 mode of action, and (6) risk assessment and mode of action.

Ah Receptor Mechanism. Mr. Clewell stated that the dioxin poster was a good example of useful risk assessment characterization research. He mentioned the work on establishing the TEF approach and praised the focus on a biochemical entity of concern for a number of environmental chemicals instead of being subject to the whims of risk assessment priorities. The project points out the fundamental dose-response information of a potentially large variety of chemicals. Dr. Symanski reiterated that this project is a clear example of how a research output has informed the risk assessment process and considerably reduced the uncertainty in that effort. In addition, it is a very clear example of a well-coordinated effort because it involves scientists both within EPA and from external agencies.

Oxidative Stress. Remarking that he learned a great deal from looking at the posters and visiting with the scientists, Dr. Buckley asserted that this research area has very significant potential to uncover the uncertainties associated with the role of oxidative stress in health outcomes. He was particularly struck by the work in this area within the Agency, which extends from the molecular level all the way to human epidemiologic studies. The research program spans a dynamic range of well-coordinated activities to answer the question of the MOA of oxidative stress in a variety of significant public health outcomes. Dr. Klaunig viewed the research as a needed area within the mechanism environment; oxidative stress appears to play a role in a number of chronic and acute diseases, including diabetes, neurodegenerative diseases, cancer, heart disease, and

ischemic injury. This team of scientists seems to be well aware of the potential problems related to measurement, and the data generated thus far appear to be very good. Another strength is the researchers' attempts to improve the predictive value of the biomarkers of oxidative stress in humans. Dr. Jayjock's response to the posters was very enthusiastic. This research is an outstanding example of a broad-based mechanistic approach rather than an approach that examines specific chemicals.

Luteinizing Hormone Disruption. Mr. Clewell stated that the work is an excellent example of hypothesis-driven research. He was particularly impressed by the forward thinking of the group in understanding the impact of the MOA and the effect of the chemical in animals and humans. This extremely well thought out research area has been very productive in influencing the regulation of atrazine. Dr. Buckley raised a question about the relevance of the dose regimen relative to environmental exposures. The experiments are being done at concentrations that have no environmental relevance; even though they are elucidating the mechanism, their importance or value is in question if they are outside the realm of what can occur within human populations. Dr. Landolph stated that the high doses are justified, but one must determine the environmental doses to prove a dose-response. Mr. Clewell stated that if the MOA involves cumulative damage or disruption over time, then higher dosing could elucidate information about lower exposure over a lifetime. It is more problematic when looking at reproductive and gestational effects. Dr. Landolph reiterated Dr. Buckley's point that at the lower doses, the mechanism could change.

Mixed Mode of Action. Dr. Landolph indicated that he was very favorably impressed by this program, which has made enormous strides in elucidating the MOA of arsenic carcinogenesis. The research examines the methylated species and uses the common assay to demonstrate DNA damage. It also reveals collaboration between the basic mechanistic work and the physiologically based pharmacokinetic (PBPK) work. The Office of Water (OW) and the Office of Pesticide Programs (OPP) are involved in this research. Dr. Klaunig echoed Dr. Landolph's comments and asserted that this group is one of the leaders in arsenic research. Dr. Landolph noted that the group has won a number of awards for its publications.

p450 Mode of Action. Dr. Klaunig remarked that this research has great applicability from the standpoint not only of potential exposure from the environment but also of pharmaceutical use as antifungal agents in humans. This group has asked several questions about liver carcinogenicity, thyroid carcinogenicity, and reproductive effects. The hypothesis is not as clear-cut as the researchers originally thought, but they addressed that issue and are following through with additional studies. The rat thyroid tumor type is important for a number of compounds that seem to be involved in p450 metabolism. The scientists have taken a very effective approach to liver tumor induction as well as reproductive effects; the approach includes genomics and basic metabolism biochemistry. Dr. Landolph echoed Dr. Klaunig's comments and mentioned the senior leadership of Dr. Stephen Nesnow in this multidisciplinary area. This group will elucidate novel mechanisms of thyroid carcinogenesis, and the program meets a basic science and regulatory need.

Risk Assessment and Mode of Action. Dr. Clark stated that the team is very much in tune with the needs of decision-makers, is sensitive to both noncancer and cancer endpoints, and

understands the sensitivity of the issues and the limitations of the data. In terms of the balance between core-driven science and problem-driven science, this team of researchers upholds risk assessment and understanding MOA as a core capability. Dr. Jayjock echoed Dr. Clark's sentiments. The overarching approach was to use the scientific information to determine the concentrations at which rats were being exposed. The multidisciplinary team approach uses genomics and other biological mechanisms to arrive at environmental concentrations, and the models were treated from a scientific perspective. The management of this program is first rate with regard to getting "the most bang for the public health buck." Dr. Landolph summarized that the panelists liked the team approach, the senior leadership, the multidisciplinary approach, and the creation of some novel basic science.

The discussion of the LTG 1 posters continued during the working lunch. Dr. Clark encouraged the panel members to express their concerns honestly and truthfully.

Dr. Landolph asked whether the oxidative stress group will split off and undergo the same type of review as the other groups. Dr. Pearson referred to the strong interactions across other groups in addressing generic issues. Dr. Hugh Tilson described the planning process involved in the formation of the groups.

Dr. Klaunig asked how ORD addresses emerging issues, for example, nanoparticles, in terms of incorporating such issues into the MYPs. Dr. Preston answered that an investigator in his Division would initiate a small preliminary effort in the case of such an issue. By revisiting the MYPs on a regular basis, emerging issues can be incorporated. Dr. Klaunig asked whether the emergence of a major environmental issue is handled from the top down or the bottom up. Dr. Preston replied that the approach falls somewhere in the middle. His Division has a small set-aside of funds for new initiatives. For more comprehensive issues, the Agency establishes task forces.

Dr. Symanski asked how, given the limited pool of resources, decisions are arrived at in the case of emerging issues when competing requests are made at the Division level. Dr. Preston explained that the HHRP's implementation team is responsible for ensuring that the human health research portfolio covers all of the necessary issues. That group would suggest a movement of issues within the MYP. A participant mentioned the RCTs, which reach a consensus after a dialogue about competing demands. Dr. Clark added that data acquired from one project (air monitoring) can be used in another project (susceptible populations). Dr. Tilson remarked that the extramural grant program deals with these issues.

Dr. Landolph asked whether the oxidative stress group will grow substantially in the next 10 years. Dr. Preston responded that the question is whether oxidative stress is observable at low concentrations. If it is a low-dose phenomenon, then the group might expand. The issue might evolve into a collaborative core.

Dr. Klaunig asked whether there were other issues regarding LTG 1, and he inquired about whether the panelists were addressing the charge questions. Dr. Clark stated that the BOSC is interested in three themes: (1) interaction with stakeholders, (2) leveraging with other agencies to

avoid duplication, and (3) communication. All of the charge questions are consistent with areas that the BOSC has evaluated in the past.

After Dr. Klaunig read the questions involving relevance, Dr. Buckley mentioned that no information has been forthcoming about the extent to which this concern dovetails with the work of other agencies. Dr. Landolph mentioned two pieces of information: technical collaboration with the National Institute of Environmental Health Sciences (NIEHS) and the extramural grants program. Dr. Klaunig added that the conazoles researchers have worked with industry, but there does not seem to be collaboration with other agencies, such as the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC). A number of the panelists voiced opinions about the evidence of collaboration across the LTGs and the need to address this issue as an overarching question of the HHRP. Dr. Klaunig noted that in the conference calls, flowcharts indicated the interactions, but that information has not been transferred to the poster sessions. Dr. Buckley reiterated that information about the way in which the oxidative stress program dovetails with the work of NIH or CDC is absent. When Dr. Landolph stated that the information should be funneled to Drs. Tilson and Preston, Dr. Preston stated that he knows about all of the collaborations involving his Division and that the PIs are aware of the interactions across agencies and even internationally. Dr. Clark pointed out that the MYP includes a goal-by-goal description of interactions with other groups inside and outside the Agency. Dr. Preston stated that those interactions take place on a "small-level," and Dr. Cupitt added that they occur on a case-by-case basis. Dr. Symanski asked whether formal memorandums of understanding (MOUs) have been established related to the activities of scientists. Dr. Cupitt responded that EPA has MOUs with the National Aeronautics and Space Administration and the Department of Energy. Dr. Klaunig asked whether information about the MOUs is readily retrievable so that the panelists can address that part of the charge.

In response to a question from Dr. Landolph, Dr. Clark stated that the BOSC wrote the charge questions. After Mr. Clewell mentioned that talks at an organizational level are critical and the first set of posters did not display clear examples of collaboration, Dr. Preston mentioned that the presenters were given the charge questions only indirectly. When Dr. Cupitt mentioned that the panelists could recommend collaborations, Dr. Klaunig cited the problem as being that the panel does not know whether collaborations are involved in the posters. The panel would like a concise list of collaborations. Dr. Buckley mentioned that this issue should be dealt with when it is introduced. How is overlap with other agencies identified? What is the process by which redundancy is minimized? In addition, the PIs can be asked how they avoid redundancies.

Dr. Klaunig mentioned that the issue in regard to LTG 1 will be addressed after the fact. The second element of the charge involves quality. Regarding the process whereby funds are allocated, Dr. Zenick explained the use of internal requests for proposals. Dr. Cupitt mentioned the use of external panels for peer review and quality assurance on a 3-year basis. Dr. Symanski asked whether the review process for existing programs is common across Laboratories and Centers with ORD. Dr. Cupitt answered that the review is done on a 3-year cycle as an external peer review; the details vary, but the goals are consistent across the Laboratories and Centers. In response to a question from Dr. Symanski, Dr. Cupitt stated that the Laboratory directors establish the criteria for the review. Dr. Reiter noted that ORD reviews take place at the Division level on a 4- to 5-year cycle. The second round of the divisional reviews was just completed. The

first round focused only on quality of science. Impact and leadership also must be examined, and that stipulation is written into the charge to the peer-review group.

Dr. Klaunig stated that the performance criterion is clearly defined. The use of output by stakeholders comes from the testimonials and the abstracts. The progress to meet the LTGs also can be addressed based on the posters. Scientific leadership likewise can be considered by the panel.

When Dr. Clark mentioned that the bibliography is arranged by LTGs, Dr. Buckley raised the question of needing a denominator. In response to a question from Dr. Klaunig about other information needed to help address the charge questions, Mr. Clewell mentioned that nothing in the charge addressed the question of organizational impediments to the progress of the scientific research. A residual issue concerns the compartmentalization that is often involved in research and that compromises the efficiency of an organization. Dr. Klaunig asked Mr. Clewell to capture his comments in writing. Dr. Zenick mentioned PI-to-PI interactions across organizations. The MYPs create the opportunity to work through synergies. Dr. Reiter added that in the development of projects, additional weighting is given to programs that cut across organizations. Mr. Clewell reiterated that this serious organizational issue is not adequately addressed in the materials and should be documented.

HHRP LTG 2: Aggregate/Cumulative Risk

LTG 2: Overview—Aggregate/Cumulative Risk

Dr. Jerry Blancato, NERL/ORD/EPA

Dr. Jerry Blancato stated that LTG 2 is a difficult goal that supports the needs of scientists and regulatory agencies. Risk assessors and risk managers use methods and models to characterize aggregate and cumulative risk. The goal is to reduce risk from exposure to multiple environmental stressors. The key research questions are as follows: (1) What are people's real-world aggregate exposures? (2) What contributes to aggregate exposures? (3) How do we measure, model, and/or predict cumulative risk from aggregate exposures? (4) How do we mitigate aggregate/cumulative risk?

Aggregate exposure refers to the combined exposure of an individual or defined population to a specific agent or stressor via relevant routes, pathways, and sources. Aggregate risk is the risk resulting from aggregate exposure to a single chemical or agent. On the other hand, cumulative risk refers to the combined risks from aggregate exposures to multiple agents or stressors. The Food Quality Protection Act (FQPA) uses a narrower definition, that is, multiple route exposures to multiple pesticide residues and substances that have a common mechanism of toxicity.

The research approach, as displayed in the posters, is to identify and implement cost-effective ways to measure exposure, develop methods and models to characterize aggregate and cumulative exposures and risks, and understand the effects of mixtures of environmental stressors with similar and dissimilar modes. This approach entails two broad topic areas: (1) developing and validating tools to better address the complex issues and (2) applying and

testing the tools in specific case studies that also aid the Agency in achieving its programmatic mandates. The tools referred to are the mechanisms to do the assessments.

The posters show the development of new analytical methods for chemicals and their biological metabolites and the development of new methods to determine the bioavailability of selected chemicals in different media. In addition to the development of new methods, the posters include measurement studies designed to characterize real-world aggregate exposures and provide high-quality exposure and exposure factor data. Examples of these measurement studies include the National Human Exposure Assessment Survey, Children's Total Exposure to Pesticides and Other Persistent Organic Pollutants, and Children's Environmental Exposure Research Study. The results of some of the studies are displayed in the posters that deal with databases and repositories, such as the Consolidated Human Activity Database, Human Exposure Database System, and Exposure Factors Handbook. Other posters cover models and computational techniques, such as the Stochastic Human Exposure and Dose Simulation Model, Exposure-Related Dose-Estimating Model (ERDEM), indoor fate and transport, and computational method to explore the interaction of chemicals in a mixture of pesticides having a similar MOA.

After describing several posters on case studies and risk assessment applications of aggregate and cumulative risk, Dr. Blancato described the impact of the research. New tools have been developed and evaluated for characterizing exposures, and the tools are readily available to the scientific community. The value of the tools has been demonstrated through the case studies, and the tools have been used to address specific ORD, Program Office, and/or Regional Office science needs.

In response to a question from Dr. Buckley about the charge questions involving coordination across agencies and organizations, Dr. Blancato explained that much of the work starts at the scientist level. Regular meetings occur with the federal community on specific issues to determine priorities. Through the STAR program, ORD researchers interface with external collaborators. However, there is no formal process for converting MYPs into multiagency plans.

In response to a question from Dr. Jayjock, Dr. Blancato stated that the work with Dr. Lawrence Berkeley appears in one of the posters but not in detail.

Discussion

After viewing the LTG 2 posters, the panelists reconvened to discuss the group of 17 posters. Dr. Jayjock commented on the remarkable body of work represented by the posters. He agreed with the emphasis on analytical methods regarding exposure assessment. However, the program lacks source characterization and instead seems to focus on pesticides and specific analytes and toxicants, whereas regulatory initiatives in Europe and Canada include other materials. EPA should be involved more directly at a higher level in that effort.

Dr. Buckley asked to what extent measurements are represented in the program. Dr. Jayjock stated that the measurements are approved analytic methods and the analytes are fairly focused and limited.

Dr. Landolph stated that he was impressed by the dioxin work done by the Agency. He supports the attempt to address environmental levels of dioxin and cancer risk. He also mentioned the additivity study and the ERDEM study.

Mr. Clewell noted the impressive range of activities associated with the posters on case studies and risk assessment applications of aggregate and cumulative risk. The research will pay off years from now. Mr. Clewell raised a question about why pyrethroids are not considered part of core research. Dr. Blancato explained that the work was initiated through a cross-laboratory initiative, but as an important, fundamental part of the work, it is now in the core research program. Mr. Clewell stated that he was pleased with the excellent interactions between laboratories as evidenced by the posters. Dr. Clark concurred and stated that the first poster gave a good description of a network within the Agency to exchange ideas across the Laboratories. A significant amount of interaction occurs inside the Agency, but there does not seem to be any formal work outside the Agency. Dr. Klaunig called for the incorporation of these comments into the draft report.

Dr. Buckley stated that he was impressed by the interaction within the Agency and outside the Agency, especially with respect to the dioxin issue and organophosphate pesticides. In contrast, there seemed to be no drinking water office representation within the research authorship. In the context of the drinking water issue and cumulative exposure, is it relevant to consider some of the stressors that may not be within the realm of EPA's mandates? For some of the health outcomes for which the chemical stressors are considered, physical stressors such as noise and psychosocial stressors might be involved in the manifestation of disease. The question involves the extent to which those research components should be considered. Dr. Clark raised the question of whether the approach could be applied to biological agents as opposed to chemical agents. Dr. Cupitt stated that a program in drinking water is looking at pathogens and microbials to examine their impact. A number of biological indicators are being developed, and genomics and proteomics are being used. The work in human health under the core research area concerns using a systems biology approach to examine the cascade of events leading to an effect.
Dr. Landolph asked whether the recommendations of the Science Advisory Board (SAB) Drinking Water Committee filtered down to the PIs involved in drinking water research.
Dr. Reiter cited an effort to make those recommendations part of the discussion about the research program, and Dr. Jane Ellen Simmons, a drinking water investigator, confirmed that the draft report was consulted in discussions.

Dr. Zenick responded to Dr. Buckley's comment on other types of stressors. Over the past 3 to 4 years, discussion in the Agency has shifted to the issue of health disparities and the factors that contribute to it. The topic is ideal for a grants program. Activities are under way for the multistressor approach to the issue.

Dr. Landolph stated that he was very impressed by the pesticide poster examining the question of additivity because of the uncertainty about mixtures. Dr. Klaunig reiterated that these comments should be captured for the draft document.

Discussion and Work Session—Work on Draft Report

Dr. Klaunig called for the panelists to use the charge questions (relevance, quality, performance, leadership) as guidance to address the LTGs. Regarding the written report, Dr. Jayjock has a draft, which he will revise in light of the poster presentation and discussion and comments from the other members assigned to LTG 2. Dr. Landolph stated the same for LTG 1. Dr. Klaunig suggested that the writers follow the four topics in the charge and add another topic if needed. Dr. Clark mentioned that the charge subquestions can be generalized and folded together, and the panelists can work together in groups of three. The panelists agreed that the four LTG documents would be available by Tuesday night. Dr. Klaunig called for the drafts to elucidate strengths and weaknesses. In terms of program resources prioritization, Dr. Clark pointed out the need to cite specific priority items that are not being accomplished. Because Dr. Klaunig had to leave the meeting Tuesday night, Dr. Landolph agreed to undertake the overall general response on Wednesday when a short summary of the major points would be delivered.

Dr. Klaunig asked the panelists to consider anything that would improve the review process in the future in terms of logistics, materials, and so on. For example, the poster sessions affect the time spent on podium presentations. If they are helpful, would it be better to allocate more time to view them? The panelists then discussed the turnaround time for the draft report.

Dr. Landolph raised the question of the retirement of key leaders in the program and the need for replacement and training strategies. It was determined that this topic should be covered under leadership. Dr. Clark mentioned constraints in the recruitment and training process that make it impossible to fill senior positions for national program managers. Dr. Landolph asked whether self-motivated, creative people can prosper in this system and whether bureaucratic obstacles to success exist. Dr. Clark responded that there are significant opportunities for people to take key roles.

Adjournment

The meeting adjourned for the day at 4:55 p.m.

TUESDAY, MARCH 1, 2005

Review of Prior Day's Activities
Dr. James Klaunig, Chair, Human Health Subcommittee

Dr. Klaunig welcomed the participants to the second day of the meeting and asked the subcommittee members to repeat the roll call. Dr. Mattison, from The National Institute of Child Health and Human Development, joined the group. To review the prior day's activities, Dr. Klaunig noted that the panelists agreed that they had an adequate amount of time to review the posters; they are working on their draft written reports. Today's working lunch will be replaced by work group sessions.

HHRP LTG 3: Susceptible Subpopulations

LTG 3: Overview—Susceptible Subpopulations
Dr. John Vandenberg, National Center for Environmental Assessment (NCEA)/ORD/EPA

Dr. John Vandenberg stated that the topic of susceptible subpopulations underlies much of ORD's research across the board. Risk assessors and risk managers use ORD's methods and models to identify susceptible subpopulations, which in turn reduces the risk of susceptible humans exposed to environmental stressors. The key research questions for susceptible and highly exposed subpopulations and life stages are as follows: (1) What subpopulations have differential risk to environmental stressors? (2) What is the basis for differential risk? (3) What is the risk to susceptible subpopulations? and (4) How can differential risk be mitigated?

The factors affecting susceptibility include intrinsic factors (e.g., life stage, gender, genetic factors), acquired factors (e.g., preexisting disease, nutrition, stress, behavioral factors), and other factors such as occupation, location of residence, and activity patterns that place individuals in contact with environmental agents. EPA's intramural focus emphasizes life stage (i.e., children's health), preexisting disease (i.e., asthma), and activity patterns. EPA's grants and Centers focus on genetic and acquired factors in children.

The research areas and topics presented in the posters can be categorized according to life stage, preexisting disease, and assessment and management. After reviewing the seven research topics (children and pesticides, source-to-effects modeling, the National Children's Study, aging, asthma, children, and unique populations), including the approach of each and examples of their accomplishments, Dr. Vandenberg explained the alignment of the research questions with the topics. The panelists were asked to review 34 posters for LTG 3.

Dr. Clark asked Dr. Vandenberg how the suite of programs and the focus interact with the endocrine disruptors program. Dr. Vandenberg mentioned that the question leads to a broader point involving the complementary nature and interplay between susceptible subpopulations and other research in the Agency.

Dr. Landolph asked about outreach and the impact of the program in the regulatory sector, in particular regarding ozone in Los Angeles and the study of the inhibition of lung capacity in

children. Has ORD been able to influence the regulatory sector regarding this type of problem? Dr. Vandenberg replied that the research in question is from the particulate matter and air programs, which examine childhood lung development. ORD's work on susceptible subpopulations complements and shares common ground with that work. The posters show that the research products are used by the Program Offices.

Dr. Mattison asked Dr. Vandenberg to talk more broadly about functional endpoints, such as pulmonary development, that develop across aging and growth. Dr. Vandenberg responded that the research related to functional endpoints is evaluated when chemical-specific assessments are created. The information is used to decide the critical endpoint. In some ways, the product process feeds into the Integrated Risk Information System assessment document to understand fundamentally how to interpret and use the information in risk assessment. Information flows through the Agency to support the regulatory programs. The development and publication in peer-reviewed literature of critical information is brought to bear in risk assessment.

Dr. Buckley asked for the rationale underlying the selection of children and asthma as foci of the susceptible subpopulations topic. Dr. Vandenberg responded that ORD studied the history of influences on the Agency. The Agency processes information from the NRC, SAB, Administration priorities, and congressional influence. All of that information is considered in the planning process. Research planners, scientists, managers, and executive leadership engage in discussions to decide about the focus of the research.

Dr. Symanski asked about the new focus on aging. Was there an attempt to evaluate activities at other federal agencies to reduce redundancies at that level? Dr. Vandenberg responded that this type of activity takes place at crosscutting meetings during the planning process. Dr. Zenick added that an interagency working group was convened to study the issue of environment and aging. Public health agencies have not considered the potential contribution of environmental exposures to risk for the older population. A dialogue with these agencies has helped to shape the focus of EPA's program. The Department of Housing and Urban Development (HUD) and the Department of Transportation have a keen interest in the topic.

Dr. Landolph asked another outreach question regarding California. In discussions with regulators, has ORD addressed the population growth problem from the point of view of public transportation and hybrid cars? Dr. Vandenberg stated that the states are responsible for dealing with this issue, and alternative strategies must be considered. ORD research results are provided to support optimal planning in the states for alternative strategies. ORD has an active relationship with California in terms of the research program. Dr. Vandenberg asserted that ORD provides the science needed to make good decisions, but the states are responsible for the actual decision-making.

Dr. Buckley stated that risk management is a large component of LTG 3. The MYP indicates that by 2020 unacceptable risks of cancer and other significant health problems from air toxic emissions will be eliminated for at least 95 percent of the population. The MYP takes an additional step to identify the way in which the information fed into the Program Offices will result in risk reductions. Dr. Vandenberg responded to this comment by referring to the need to

revisit the MYP. ORD has opportunities to identify risk reduction approaches. Its focus is on developing the science base to enable key approaches to mitigating risk.

Discussion

After viewing the posters, the panelists returned for a discussion of LTG 3. Dr. Buckley disclosed that he received funding as a new investigator through the NIEHS Children's Center program at Johns Hopkins University. As a result, he recused himself from considering the posters related to the Children's Center.

Dr. Buckley commented on the substantial set of research themes represented by the posters on LTG 3. He expressed concern with the process that determined the focus on children. Children are no doubt an important susceptible subpopulation, but the way in which the focus was determined is not well justified. Susceptible subpopulations point to an important public health issue, especially related to the environment. The process, as explained by Dr. Vandenberg, is fairly convincing, but what is the health benefit of focusing on children versus chronic obstructive pulmonary disease as it relates to airborne particulate matter? An analysis is missing that would balance or compare different kinds of health assessments.

Dr. Jayjock stated that some susceptible subpopulations that experience the most exposures, namely individuals with occupational exposure to pesticides, are not considered. At times, "the regulatory silos are allowed to get in the way of doing the science." Dr. Jayjock agreed with Dr. Buckley that a more rationalized process is needed to determine susceptible subpopulations.

Dr. Clark expressed his disagreement with this idea. He admitted to not seeing a stated rationale, but he asserted that, using the background theme of reducing uncertainty in risk assessment and determining behavioral or cultural activities that change the exposure rate, a rationale does exist for looking at activities that change exposure, particularly regarding fish consumption among Native Americans in Minnesota and the World Trade Center population. If one follows the exposure/dose-response paradigm and studies activities or subpopulations with an exposure outside the typical assumption, a rationale does exist with the theme of reducing uncertainty.

Dr. Buckley agreed that a strong rationale exists for looking at children, but he asked how that rationale compares with the rationale for considering occupational exposure to pesticides. Could a better health benefit result if that particular susceptible population was examined? Dr. Zenick countered that a fairly careful process was used to determine the focus of LTG 3. The National Institute for Occupational Safety and Health (NIOSH) was consulted on various issues, but EPA decided, given its limited resources, to target its efforts on life stage. Dr. Buckley stated his understanding that the regulatory authority for protecting worker health and safety with respect to pesticides lies with EPA not NIOSH.

Dr. Michael Firestone, from the Office of Children's Health Protection (OCHP), stated that the pesticide program looks at occupational exposure and risk. The question is whether a small percentage of the population of children is at risk or whether the entire population is at risk but at a certain period of time. Children as a susceptible subpopulation is a critical area of importance

because of the uncertainty about how children are different, especially during development and early childhood, and how that factor relates to health problems later in life.

Dr. Mattison stated that he asked two questions of the scientists at the poster session: Why focus on this particular group? and To what extent can the result of the research be extrapolated to future subgroup approaches? He reminded the panelists that the legislative focus on children mandates that the Agency attend to this subpopulation. He was reassured that the approaches used to reduce uncertainties in children can be extrapolated to the next health endpoint and vulnerable subpopulation. However, Dr. Mattison questioned whether the Agency has the breadth of health capability understanding to move to an unanticipated health consequence.

Mr. Clewell stated his agreement with the emphasis on early life. A great deal of potential toxicity has been overlooked in the past. EPA is focusing on children's health because the early life effects of chemicals have not been characterized sufficiently. The data gap might be filled by this important emphasis. Dr. Buckley reiterated that the issue is not the focus on children but the fact that a rationale is needed for the consideration of other susceptible populations from the point of view of the health benefit involved.

Dr. Landolph stated that he was impressed by the magnitude of the effort displayed in the posters and EPA's unique capabilities in analytical chemistry, melding geography with epidemiology, and using satellite data to find air pollutants. He suggested that a small parallel effort might look at a few other substances.

Dr. Klaunig asked the panelists to capture their comments in writing and convey them to Dr. Buckley. In the discussion that followed, each of the leads and secondary reviewers reported on their reactions to the posters.

Pesticides and Children. Dr. Mattison described the integrated, crossdisciplinary approach displayed in the posters, which examined changing practices in pesticide use, built exposure paradigms to respond to those changing practices, and presented a biological perspective to characterize health effects. An area that might benefit from additional discussion involves methods of tracking emerging chemical use within this area. Dr. Buckley underscored Dr. Mattison's comments by saying that the work is providing fundamental tools to assess exposure in terms of methods and modeling. The PIs are providing leadership in developing methods that researchers outside EPA can use to better assess exposure and susceptibility within this group. Dr. Buckley was impressed by the apparent lack of barriers to crossdiscipline interaction, which is seen as a positive component of the research. He added that EPA is beginning to value community-based participatory research but expertise in this area is needed. However, because some of the grantees possess that expertise, it can be obtained through extramural research funding.

Source-to-Effects Modeling. Mr. Clewell praised the structure of the work exemplified by the posters, which elucidated important information on pharmacokinetic differences in early life. An opportunity to examine pharmacodynamics using systems biology approaches is available now with the creation of the NCCT. Mr. Clewell applauded the extension of the research from children to the aging population. Dr. Jayjock stated his appreciation of the pharmacokinetic

modeling and applauded the manner in which data have been mined for application elsewhere. After praising all three of the posters, Dr. Jayjock pointed out the need to study severe near-field exposures. Dr. Mattison praised the work of Dr. Bob Sonawane and his colleagues as a remarkable contribution to the literature.

National Children's Study. Dr. Clark stated that, from a programmatic point of view, a legislative mandate calling for cooperation, leveraging, and interaction has been carried out to a high level, as evidenced by the posters on this topic. He was impressed by EPA's planned technical input over the 20-year period of the study, by the study's quality assurance and data management efforts, and by its application of the data to the real world. Dr. Landolph expressed confidence that this program will have a positive effect on reducing or mitigating factors that adversely affect children's health. He noted that this "experiment in progress" has enormous potential, peer-reviewed studies might appear in 7 years, and the study will look at birth defects and prenatal exposures. Dr. Mattison praised the high-quality contributions to the National Children's Study from EPA scientists.

Risk Assessment/Risk Management. Dr. Jayjock commented on the five posters included under this topic. He mentioned the interactive multidisciplinary approach, gap analysis, and "crossing the silos at an operational level." He also commented on the idea of exposure reduction versus risk reduction and suggested that the Agency consider the need for a more generalized approach to the issue of hard-surface cleaners in schools. A broader taxonomy will be useful.
Dr. Symanski echoed Dr. Jayjock's comments and noted the Agency's effectiveness in risk management decisions. She also mentioned that some of the work done in this program might serve the needs of activities in other programs.

Aging. Dr. Landolph noted that several interesting questions are posed by this topic. The elderly are a susceptible population in terms of infectious disease and toxins. The posters focused on the adverse health effects of benzene, arsenic, and pesticides in older adults. These studies have the potential to unearth some unique adverse health effects from specific substances. In response to a question from Dr. Buckley about particulate matter in aging, Dr. Landolph stated that particulate matter will have almost certain impacts because of its cardiovascular and pulmonary effects in the aging population. Dr. Landolph noted the enthusiastic leadership of Drs. Andrew Geller and Linda Birnbaum. He suggested that the leaders of the National Children's Study and the aging program confer about the commonalities and approaches of their programs.

Asthma. Dr. Symanski cited reports of the increased incidence of asthma and upheld EPA's rationale for studying asthma as an endpoint. The Agency has the opportunity to be a major contributor to the field in this area. The research plan lists five contaminants. Regarding bioaerosols, the research activities span the source-to-effects continuum. One of the strengths of the program is the integration of epidemiologists with basic scientists and engineers. Several of the investigated endpoints suggested a biological basis for asthma related to oxidative stress. This finding presents an opportunity for enhancing linkages with the basic scientists involved in the oxidative stress group supporting LTG 1. Regarding ORD's primary mission to carry out basic science that informs the risk assessment process, this research successfully forms the foundation for both ozone and particulate matter criteria. The results of this work also have been used in other research activity, and there is clear evidence of collaboration within ORD and

successful partnerships with NIH and HUD. One suggestion is to enhance collaboration with scientists dealing with oxidative stress. Dr. Klaunig agreed with Dr. Symanski's assessment and added that the scientists should concentrate on the current work; widening the focus to include pesticides might over-extend the effort. In addition, Dr. Klaunig noted that there appears to be interaction, but journal clubs or group meetings might be beneficial. Additional expertise is needed and would contribute significantly to the projects devoted to oxidative stress. ORD's partnering with HUD, NIH, and other agencies should be applauded. Dr. Landolph reported that the overview poster demonstrates an effective collaborative group with interesting findings. Dr. Symanski reiterated that this group focuses on risk management and evaluating appropriate intervention strategies for reducing exposures to bioaerosols.

Uniquely Vulnerable Populations. Dr. Buckley pointed to the very impressive work being done on this topic with strong interdisciplinary interactions and innovative methodologies to identify highly exposed population groups. This work goes to the heart of the environmental justice issue. The poster related to the World Trade Center shows leadership in providing a model to evaluate these kinds of situations in the future. Dr. Clark spoke about the posters related to the Children's Centers and noted a strong degree of interaction between the efforts under way in the National Children's Study and other activities. The studies funded by the Children's Centers in New Jersey and California show the manner in which information from laboratory studies was applied to assessments in the field. The programs also entail adaptability. Dr. Buckley added that some of the programs are involved in community-based participatory research, for example, the border studies.

HHRP LTG 4: Evaluating Public Health Outcomes

LTG 4: Overview—Evaluating Public Health Outcomes

Dr. Hal Zenick, NHEERL/ORD/EPA

Dr. Zenick presented information about LTG 4—to evaluate public health outcomes. Risk assessors and managers use ORD's methods and models to evaluate public health outcomes to aid EPA in determining the effectiveness of its regulatory management decisions and actions. The key research questions for evaluating public health outcomes are as follows: (1) What public health outcomes might be examined in conjunction with Agency regulatory decisions and actions? and (2) What approaches and tools are needed to evaluate (and attribute) changes in such public health outcomes to Agency actions? Dr. Zenick explained the Human Health Research Strategy diagram, which includes three components: (1) assessing risk, (2) informing risk management options, and (3) assessing the effectiveness of decisions. He reviewed the emergence of the concept of accountability in public health and referred to the EPA Report on the Environment and CDC's National Environmental Public Health Tracking Network. The 2003 draft report identifies the measures and indicators to report on the status of national environmental conditions and trends and their impacts on human health and the Nation's natural resources. The report also discusses the challenges that the Nation faces in improving these measures and includes a comprehensive draft "Report on the Environment Technical Document." In addition, the draft report provides the basis for identifying key data gaps. The second report on the environment will be released in 2006 and will focus on primary

stakeholders and a more thorough analysis and prioritization of the data gaps. Substantial input from sister agencies will be sought in finalizing the second draft report.

Another signature event that occurred in 2003 was the signing of an MOU between the Department of Health and Human Services (HHS) and EPA. The MOU is a long-term commitment to advance efforts to achieve mutual environmental public health goals; strengthen the bridge between the environmental and public health communities; and achieve better understanding between environmental hazards, ensuing exposures, and health effects. The cornerstone is crossinstitutional initiatives to link environmental and health information sources, such as EPA's National Environmental Information Exchange Network and CDC's National Environmental Public Health Tracking Network.

Current EPA-CDC collaborations are engaged in ongoing assessments of environmental and health data needs, an information exchange on data standards technology and architecture structures, discussion and implementation of potential pilot projects to examine specific data sets, and initiation of proof-of-concept projects.

After describing the extramural and intramural components of ORD's accountability initiative, Dr. Zenick commented on bridging the chasm between public health and the environment. In the past 4 or 5 years, new partnerships have evolved with new enthusiasm and commitment that recognizes EPA as a public health agency.

Dr. Mattison mentioned the Healthy People process and asked how EPA's activities link with that initiative. Dr. Zenick responded that some of the target areas align and it is hoped that the environment will play a more substantive part in the 2020 goals. Dr. Zenick stated his impression that the environment is "low on the list" of HHS concerns involving contributing factors to health.

Dr. Buckley asked whether the outcome of LTG 4 could evolve so that improvements in research could be tracked and the investment yielded in terms of public health could be determined. Dr. Zenick explained that the tracking method will identify some pivotal areas in which improvement is needed, and predictive models will be developed to determine improvements in public health. In response to a question about the Toxics Release Inventory (TRI), Dr. Zenick stated that the TRI was used to test hypotheses rather than to generate them.

Dr. Symanski stated that the MYP involves three annual performance goals related to the LTG. One goal is to identify public health outcomes that could be used to evaluate the effectiveness of decisions made by the Agency. What criteria will be used or in what framework will that decision be made? Dr. Zenick stated that the thinking has changed since that goal was established. Now it is extremely important to understand the criteria to link exposure to outcome. Dr. Symanski cited the limitations in the ability to link routine monitoring data with routine public health surveillance data. Limitations exist in making inferences about the manner in which a risk management decision actually affects public health. Dr. Zenick called for proof-of-concept projects to determine predictive linkages. Dr. Clark mentioned the BOSC review of the second national report on coastal conditions, in which the most powerful statements were made on local

and regional trends, not national trends. In this regard, Dr. Zenick commented that EPA must be responsive to the decision-makers.

Dr. Symanski noted that the MYP commits relatively few resources to this program. However, the program design leverages the activities carried out in support of the other LTGs. It is not clear how the research outputs of activities and other components of ORD will feed into and serve as inputs to this program. Clear lines of communication must be established, and criteria must be developed to allow for prioritization of the research outputs generated by other programs. Dr. Zenick stated that ORD has programs in place, especially in air and water, that link to the indicators. Other programs exist in particulate matter and pesticides.

Discussion

After the panelists viewed the poster on LTG 4 and reassembled, Ms. Houk made a request for public comments. In the absence of any comments, Dr. Symanski began the discussion of LTG 4.

Dr. Symanski commented that evaluating public health outcomes is associated with EPA policies and regulations. This relatively new program is clearly consistent with the mission of EPA to protect human health and with the accountability directive issued by the former Administrator of EPA. The activities of this program and other programs in ORD are built on the source-to-disease continuum. For this program to be successful, clear lines of communication must be developed between it and the programs that support the other LTGs. The program needs to be more structured than it is now, and criteria must be developed to allow for prioritization of the research outputs from the other programs that would feed into this program. The Draft Report on the Environment makes clear that this program should develop and apply environmental indicators that reflect more than one aspect of the source-to-disease continuum. This specification is where the challenge lies. It is difficult to develop indicators that would allow the Agency to study the reduction in exposure or in levels of a contaminant in the environment and to show measurable improvement in health or reduction in disease or mortality as a result. It is particularly problematic because of the myriad of nonenvironmental risk factors that also come into play. Dr. Symanski described some of the program's successes. The program is committed to the demonstration projects to evaluate the effectiveness of a particular action or policy on a public health outcome. This case study approach is a very appropriate way to get started and will allow the program "to get its arms around" an inordinate undertaking.

Dr. Buckley agreed that this LTG is a strategic research direction for the Agency. However, a relatively small amount of resources is identified to support this activity. This circumstance should be identified. Dr. Symanski noted that this LTG crosses over all of the other efforts in ORD; the program must grow to succeed. Dr. Cupitt mentioned that the program is supported in part by the air program. Dr. Klaunig recognized the attempts at partnering but cited his concern that the program needs the involvement of additional public health experts. The investigators are well aware of the need to define a couple of specific projects and create a plan to address specific issues. This LTG cannot be easily compared with the others; a plan is in place, but it needs refinement and additional input.

Dr. Mattison commented that the posters failed to give him a sense of interactions with local or state health departments. Dr. Symanski mentioned that the PHASE project involves collaboration with CDC and several state health departments.

Dr. Buckley commented that biostatistical support will be a key ingredient for this effort. Does that support exist within the group undertaking this effort? Dr. Zenick stated that the support is modest within ORD, but substantial database management expertise exists in the Office of Environmental Information.

Relevance of HHRP—EPA Extramural Perspective
Dr. George Lambert, Robert Wood Johnson Medical School

Dr. George Lambert presented information about the Children's Centers as one of EPA's human health extramural programs. There are 11 EPA/NIEHS National Centers for Children's Environmental Health and Disease Prevention. Two of the Centers are focused on autism. The Centers are a government, academic, and parental partnership in response to national public health and research priorities.

The goals of the program are to (1) promote multidisciplinary interactions among basic, clinical, and behavioral scientists, (2) support a coordinated program of Centers, with the goal of accelerating the translation of basic research findings into clinical or intervention strategies, and (3) establish a national network that fosters communication, innovation, and research excellence.

In terms of research relevance, the disease states (asthma, neurodevelopmental issues, autism, birth defects, fetal growth, and chromosomal aberrations) are national public health priorities. In addition to traditionally studied chemicals (e.g., pesticides, heavy metals, endocrine disruptors, brominated flame retardants), the Centers study emerging environmental chemicals. The exposure populations are urban and rural and are related to the disease states of autism and asthma. The program and Centers follow an overall conceptual framework. Most have translational research from molecules to animals to man, include intervention strategies, conduct outcome-oriented research, and engage in real-world research to monitor multiple chemicals. All four of the human health LTGs are addressed in the Centers.

Research success is evidenced by publications, research highlights, and outcomes. More than 200 peer-reviewed biomedical articles and 500 abstracts and letters have been published in leading professional journals. Dr. Lambert described the research highlights, which include biomedical and technical and respiratory research, neurodevelopmental and developmental disabilities research, research in growth and development, research in gene-environment interactions, and technical advances. In terms of outcome, he described changes in behavior, decreased exposure/body burden, improved health, and effects on regulations.

The Centers also have had an impact in capacity building; leveraging knowledge, funds, and opportunities; community-based research; and communications and outreach. The current program has provided leadership in the area of children's environmental health, developed strong community-scientist partnerships at all of the Centers, trained new scientists in children's environmental health, developed new technologies and methodologies in exposure assessment

and molecular biology, and worked toward translation of best practices into community and clinical care.

The Centers, in conjunction with EPA, are national assets. They provide outreach to the country and beyond through research data, studies, and collaborations. The Centers also assist all of the environmental stakeholders and are focused on some of the highest national health priorities as defined by the people and the public health communities. In addition, the Centers interact with EPA on many levels to help EPA fulfill its role and mission.

Dr. Lambert stated that children are the canary of the species in terms of susceptibility, sensitivity, reliability, and diversity of adverse effects. He asserted that when we protect children, we protect the environment. Furthermore, children with neurodevelopmental concerns might be the most sensitive indicators for humans. For example, children with autism are trying to tell us something; we need to ask more of the right questions to learn from them.

In response to a question from Dr. Landolph, Dr. Lambert stated that autism is polygenetic. He discussed environmental chemicals and chemicals in general in terms of autism and oxidative stress toxicological mechanisms, mentioning, in particular, glutathione S-transferase. In animal studies, certain chemicals cause regression in neurological behavior. In response to another question regarding the incidence of autism, Dr. Lambert referred to a University of California at Davis study of children diagnosed with autism and neurological diseases between 1983 and 1985 and between 1993 and 1995. A 207 percent increase was demonstrated between the two time periods. Children's neurological diseases should be studied from the point of view of their interrelationship with environmental chemicals.

Dr. Mattison asked how the Centers give information to EPA from lessons learned about children's sensitivity to environmental exposures. Dr. Lambert responded that the two autism Centers take slightly different approaches. The New Jersey Center conducts home health surveys of air, water, and soil, whereas the Davis Center takes a more polygenetic approach with a greater array of environmental chemicals.

Dr. Buckley asked to what extent intramural research is translated into the Centers, especially as related to methods of measuring exposures. Is that interaction occurring? Given the investment in the Centers and the relevance to the National Children's Study, the translation of information from the Centers to EPA and the National Children's Study is an issue. Dr. Lambert reiterated that many of the Centers have faculty on the organizing committees of the National Children's Study. The National Children's Study and EPA have asked the Children's Centers for papers about lessons learned. The expertise is being funneled into the National Children's Study.

Dr. Nigel Fields, from the National Center for Environmental Research, added some information about the way in which the intramural program interacts with the extramural program, specifically the Children's Centers. The Centers are brought together each year through a series of meetings at which intramural scientists are involved in technical discussions about new methodologies. Opportunities also exist for funding to increase the types of studies done at the Children's Centers.

Discussion and Work Session—Work on Draft Report

Dr. Klaunig reviewed some scheduling and deadline information. By the end of the meeting on Wednesday, the four LTG lead writers will give their individual drafts to Ms. Houk, who will send the materials to all of the members for comment. Comments should come back from the members by Monday, March 14. Ms. Houk will send the drafts with comments to the lead writers by COB on March 14. The lead writers should return the revised drafts to Ms. Houk by March 25. Drs. Klaunig and Clark will write the executive summary and compile the draft document for discussion and finalization during the conference call, which will be scheduled for the first full week of April. Virginia will send an e-mail asking the panelists to check their calendars regarding the conference call date. Dr. Clark mentioned that the BOSC will discuss the final draft document during its April conference call. He also stated that he will collect the top three or four points from each lead writer for the presentation on Wednesday.

The remainder of the session was spent in small group discussions and individual work on the draft report.

Adjournment

The meeting adjourned for the day at 5:30 p.m.

WEDNESDAY, MARCH 2, 2005

Review of Prior Day's Activities and Overview of Today's Agenda

Dr. James Clark, Vice Chair, Human Health Subcommittee

Dr. Clark explained that he is substituting for Dr. Klaunig, who had to leave the meeting early. He reported that the lead writers for the report finished a substantial amount of writing on the previous evening. He also mentioned that, because of previously scheduled travel, he will be unable to continue to lead the meeting and Dr. Landolph will assume that role. The panelists completed the assessment of all the LTGs during the previous day's session, began to draft the report to the BOSC, and arrived at some key points to be shared during the exit session.

Relevance of the HHRP—EPA Program Office Perspective

Dr. Randy Perfetti, Office of Science Coordination and Policy, EPA

Dr. Randy Perfetti presented the regulatory perspective on ORD's HHRP. High-quality scientific data are essential to making sound regulatory decisions, and regulatory programs such as the Office of Prevention, Pesticides and Toxic Substances (OPPTS) actively engage with ORD to achieve this goal. Dr. Perfetti's presentation covered three topics: (1) current challenges, (2) the impacts of ORD's research, and (3) future work.

The challenges in health risk assessment relate to the FQPA and the Safe Drinking Water Amendment (SDWA) of 1996, which required OPPTS and OW to produce increasingly complicated human health risk assessments. The areas of increasing emphasis for risk assessment involve highly sophisticated science and include mechanisms of toxicity, life stage sensitivities, chemical mixtures and cumulative effects, endocrine disruption, and aggregate and cumulative exposure situations. ORD contributes to each of these areas of emphasis.

In terms of mechanisms of toxicity, ORD helps OPP characterize potential health effects, determine the human relevance of laboratory animal data, inform the dose-response at levels of human exposure, and judge the potential for cumulative effects. Dr. Perfetti offered two examples of ORD assistance. ORD's research on atrazine revealed that atrazine had neuroendocrine-mediated reproductive and developmental effects. The research contributed significantly to hazard characterization, revealed a common mechanism for grouping, and allowed for a cumulative risk assessment for atrazine pesticide. It was found that atrazine's mechanism of toxicity occurs only at certain periods of maturation of an organism; therefore, ORD's research also elucidated the importance of life stage sensitivities with respect to the regulation of atrazine. Another example of ORD's contribution to the scientific knowledge about mechanisms of toxicity involves the conazole pesticides. These pesticides produce a number of effects seen in laboratory animals (e.g., liver and thyroid tumors, reproductive effects, and neurotoxicity) and are inducers of p450 enzymes. ORD is currently using state-of-the-art molecular tools supported by traditional toxicological methods to help OPP determine whether the conazole pesticides share common mechanisms of toxicity and to make decisions on the regulation of these chemicals.

In terms of chemical mixtures and cumulative risk, the FQPA required OPP to look at cumulative risk in chemicals that share a common mechanism of toxicity. The first group of chemicals to be considered were the organophosphate pesticides. The problem was how to determine each of the 30 pesticides' relative contribution to the cumulative risk. ORD helped OPP to produce a cumulative risk assessment for the 30 chemicals. A dose-response model was created to estimate the relative potency of cholinesterase-inhibiting organophosphate pesticides. The empirical mode allowed for the determination of benchmark doses for each of the pesticides and the ability to rank them according to their relative potency. Dr. Perfetti also described ORD's work in developing a PBPK model for N-methyl carbamates and pyrethroids and providing OPP with pharmacokinetic data, work for which ORD has received high praise.

Regarding endocrine disruption, the FQPA of 1996 required that EPA develop and implement a screening program to determine whether certain substances might have estrogenic effects in humans. The SDWA of 1996 enabled OW to screen for drinking water contaminants when substantial numbers of persons are exposed. ORD has conducted fundamental research in support of test development. It has looked at the relationship been molecular structure and effects on estrogen receptor for quantitative structure-activity relationship (QSAR) modeling, developed a molecular basis for antiandrogenic effects to support second-tier test development, elucidated the basic biology underlying estrogen receptor function for receptor binding protocols and QSAR modeling, examined dose-response relationships and critical periods of exposure for reproductive tests, and conducted fundamental studies on thyroid as a target.

In terms of aggregate and cumulative exposure situations, ORD has generated a number of databases to provide realistic measures of exposure, developed sophisticated exposure and dose models, and produced a variety of guidance documents, including an exposure factors handbook, risk assessment guidelines, and probabilistic guidelines.

ORD's Computational Toxicology Program is developing QSAR models that will allow prioritization and ranking of chemicals that lack toxicological data (high-production chemicals, inert pesticide ingredients, and antimicrobial pesticides). It also is providing OPP with PBPK modeling and "omics," which could lead to hypothesis-based risk assessment whereby toxicity can be extrapolated. Dr. Perfetti stated that he foresees a future in which tests will be done to look at toxicity pathways and then *in vitro* and *ex vivo* tests can be used to arrive at endpoints.

Mr. Clewell praised OPP's work in science-based risk assessment. He asked about the nature of the interaction between OPP and the laboratories in terms of working on quick-response versus long-term problems. Does OPP have access to the planning process? Dr. Perfetti noted the high-quality cooperation with the Centers and Laboratories. OPP and the Center and Laboratory administrators meet regularly to plan the long-term research. In response to a question about QSAR modeling, Dr. Perfetti stated that the work is ongoing.

Dr. Buckley noted that the effectiveness of collaboration was transparent throughout the review of the posters. However, the extent of collaboration seems to be inconsistent across the Program Offices. How does OPP enable the collaboration? Dr. Perfetti responded that, unlike other offices, OPP has 8 years of experience, close relationships among the managers, and familiarity with the involved scientists. Dr. Reiter stated that this review entails interactions that are heavily

biased toward OPPTS, but interactions also occur with other Program Offices; Laboratory directors and Office directors meet on a regular basis to develop research plans. In the past 8 to 10 years, ORD has made a concerted effort to engage in a dialogue with the Program Offices. Dr. Buckley characterized the situation by saying that the collaborations are consistently strong across the Program Offices, but the science with respect to human health is biased toward OPPTS. Dr. Reiter responded that the scientific needs are different based on the statutes.

Mr. Clewell stated that the review gave the impression of a very strong emphasis on OPP-type work. Is that a fair reflection of the level of effort? Dr. Reiter responded that ORD has a susceptible population program that looks at asthmatics and provides fundamental support for the Office of Air. The Office of Water needs to incorporate the age-related effects and life stage into its dealings with contaminants. The selection of the research agenda is intended to be broad based and to examine uncertainties that cut across the various Program Offices. Dr. Amal Mahfouz, from OW, stated that the drinking water program deals with human health, regulates a number of pesticides, and collaborates effectively with ORD and OPP on the human health and drinking water goals.

Dr. Cupitt reiterated that the ORD review covers the human health core research, which has applications across a variety of other programs. A substantial amount of human health research supports the air and drinking water programs. This particular review focuses on a portion of the human health program.

Dr. Landolph commented that the emphasis in risk assessment is swinging toward more mechanistically based risk assessments. Obviously, those will take time to develop. If there is a proposal to change from a linear to a threshold model, will the approach be conservative until a substantial database is developed? Dr. Perfetti responded that the draft cancer guidelines are based on a conservative framework.

Relevance of the HHRP—EPA Regional Perspective
Dr. David Macarus, Region 5, EPA

Dr. David Macarus presented information about regional connections to human health research. The question involves whether ORD's human health research is relevant from the Regions' view. A system of 10 regional science laboratories exists to ensure a continuum of research as the Regions attempt to apply the regulations developed by the Program Offices. A significant partnership exists between ORD and the regional offices. The collaborations entail workshops, seminars, the Regional Applied Research Effort (RARE) program, the Regional Methods Initiative, the Regional Research Partnership Program, and product expositions. ORD-regional collaborations also involve ORD projects with strong regional inputs, scientist-to-scientist connections, ORD technical advice to regions on high-priority issues, regional input into ORD planning through research coordination teams, the new Agency accountability project, and science forums and professional society meetings.

Dr. Macarus gave several specific examples of collaboration between ORD and the Regions. He described the Emerging Pollutants Workshop in Chicago in August 2003 and the Cumulative Risk Workshop in Dallas in November 2002. In addition, a number of RARE projects involved

ORD collaboration, including a project studying health risk from dioxin near an incinerator in Columbus; a project involving asthma intervention for families in Boston public housing; a project examining the effect of airborne manganese on elementary school children in Marietta, Ohio; and a project exploring body burdens of polybrominated diphenyl ethers and hexabromocyclododecane.

After describing the Detroit Exposure and Aerosol Research Study (DEARS), Dr. Macarus remarked on ORD advice to Regions on high-priority issues. Region 5 has a difficult enforcement case related to dioxin contamination and has asked ORD to help evaluate a new bioavailability study and relate the results to human impacts and risk. Likewise, the ORD accountability project is helping to answer the question of whether measurable human health outcomes result from EPA actions. Twenty pre-proposals have been submitted by the Regions.

In summary, Dr. Macarus stated that ORD's human health research is relevant from the Regions' point of view—"It is a well-traveled, two-way street."

Mr. Clewell asked whether the Regions ever "get caught in the middle" between ORD and the Program Offices. Dr. Macarus stated that good cooperative relationships exist. The question of priorities is common, but scientific problems do not occur.

Dr. Buckley asked Dr. Cupitt how ORD balances providing resources and service to the Regions with the need for scientific rigor and credibility for evaluation purposes. Dr. Cupitt reiterated the components of ORD's mission: (1) research, (2) advice and technical assistance, and (3) leadership. About 10 to 15 percent of its activity goes toward developing technical support activities for the Regions. Dr. Mattison asked how this activity is incorporated into annual performance appraisals. Dr. Cupitt stated that his Laboratory incorporates the three components of the mission into the structure of the reviews of its programs at the Division level. The promotion process explicitly evaluates those three components. Dr. Sonawane, from NCEA, added that NCEA has a performance standard to provide guidance and consultation to Regional and Program Offices.

Relevance of the HHRP—EPA Office of Children's Health Protection (OCHP) Perspective
Dr. Michael Firestone, OCHP, EPA

Dr. Firestone presented information about ORD's research in support of children's environmental health protection. Children are not really a subpopulation; childhood is a sequence of life stages. Children are not a small portion of the population; rather, children are 100 percent of us. After describing the history leading up to the creation of the OCHP, Dr. Firestone stated the Office's mission—to make the health protection of children and the aging a fundamental goal of public health and environmental protection in the United States and around the world. The key areas of OCHP are outreach and partnerships, regulatory policy and economics, science, and the aging initiative.

In collaboration with ORD, OCHP tackles the following children's environmental health issues: asthma and other immunologic effects, neurodevelopmental effects, cancer, acute poisoning, and educating parents and health providers. ORD also is active in children's environmental health

risk assessment issues involving cancer, developmental immunotoxicity, developmental neurotoxicity, exposure monitoring and assessment, practical risk reduction education, the role of endocrine disruption as an MOA, toxicokinetics and age, and the use of genomics in understanding life stage impacts on toxicity. In addition, ORD has been involved in examples of children's environmental health risk in the news. An article in *U.S. News and World Report* describes a massive new study aimed at finding out why children get sick, and a recent newpaper article reports on ORD-funded research on the way in which pollution might cause genetic changes in fetuses.

Dr. Firestone presented ORD's strategy for research on environmental risks to children, which covers the areas of risk assessment, toxicity testing, toxicology research, exposure, extramural research, and aging. General research needs include updating the 2000 children's research strategy, full implementation of the National Children's Study, and completion of the aging research strategy framework. In the area of risk assessment, the key research needs involve moving from a children's risk assessment framework to guidance, and exploring age-related differences in inhalation exposure and risk. In the area of health effects, the key research needs involve developing new methods and generating corresponding data to fill the gaps regarding early life stage toxicity, using "omics" to understand the nature and effect of possible life stage differences in toxic response, and exploring the potential links between prenatal exposure to endocrine disrupters and cancer and developmental effects. In the area of exposure, research is needed to continue to fill exposure factors data gaps and obtain biomonitoring data for children younger than 5 years of age.

Dr. Firestone concluded his presentation by stating that ORD research has provided data and methods critical to improving the assessment of children's differential environmental health risks. EPA's science inventory lists more than 570 publications related to children's environmental health. The potential for life stage sensitivity must be routinely considered in EPA risk assessments. ORD's research helps provide key data.

Dr. Hugh Tilson thanked all of the participants for their involvement in the review. He recognized the efforts of the theme leads, the topic leads, and the poster leads and thanked the speakers and support staff.

Oral Report on Charge Questions

Dr. Landolph presented the overall points arrived at by the panelists, who found the research of ORD and the HHRP to be of high quality and appropriately focused. The research was found to be multidisciplinary, displayed good stakeholder participation, informed risk assessments and achieved the goal of reducing uncertainty, and showed the benefits from peer-review expectation. The hallmarks of the HHRP are that the research is coherent and coordinated, the scientists display an overall high level of excitement and commitment, and there is a decisive propensity to encourage development of new data and mining of available data to inform the risk assessment decisions of stakeholders. However, the justification of the HHRP was not clearly articulated. ORD is doing the right research, but the conceptualization and articulation is unclear and incomplete. A more science-based rationalization and justification are expected as well as ORD ownership. Interaction is occurring between the LTGs, and this interaction should be

acknowledged and encouraged. The panel recognizes and appreciates the amount of work ORD put into the preparatory materials. There is evidence that ORD has responded to previous reviews by the Human Health Research Strategy Committee, Drinking Water Research Committee, BOSC, and NRC.

Regarding LTG 1 (mechanistic data in risk assessment), Dr. Landolph noted the effective mixture of multidisciplinary research from cell to human populations and back again. He also pointed to the leadership in dioxin, arsenic, chlorotriazines, and conazoles research applications in environmental health to support risk assessment. The panel was supportive of the incorporation of oxidative stress research into the environmental health research.

Dr. Jayjock reported on the panelists' reactions to LTG 2 (aggregate and cumulative risk). The research is coherent and coordinated, and the scientists are enthusiastic and committed. The work done on this LTG shows a propensity to mine the available data to inform risk assessment decisions. The assessments should be more comprehensive and look at a wider array of chemicals important to human exposure. At the very least, the ongoing efforts in the European Union and Canada should be engaged.

Dr. Buckley presented the panel's reactions to LTG 3 (sensitive subpopulations). The work is well grounded within ORD's Strategic Plan, and there is evidence of good coordination and leveraging across federal agencies. The research is appropriately directed, but it is not well justified by ORD in terms of the greatest public health benefit, or perhaps its justification is not clearly articulated. The current level of involvement of Program Offices, Regional Offices, and other stakeholders is adequate; it should be sustained and upgraded. ORD should expand its expertise in community-based participatory research.

Dr. Symanski reviewed the panelists' reactions to LTG 4 (public health outcomes). The panel found the research to be relevant to the mission of the Agency and consistent with the accountability directive. However, this program will benefit from interactions with the other programs, and such integration is critical for its success. The program has the potential to utilize research from the other LTGs. It is recommended that a mechanism be put in place that has both formal and informal components to promote dialogue among the LTGs and provide a process for assessing research outputs. Over time, the program will require a greater commitment of resources. An LTG to evaluate the effectiveness of risk management decisions made by the Agency is overarching, and given the magnitude and scope of the review, it will be helpful for the program to articulate more focused goals that would help guide its activities in the short term and elaborate a process that would allow it to identify, for example, which actions or policies are going to be examined, which specific endpoints are going to be studied, and which specific environmental indicator might be developed or applied to make those linkages between the risk management decisions and the endpoints.

Ms. Houk asked whether any points needed clarification. Dr. Tilson requested clarification on the justification issue. The justification for the program came primarily from external sources, but is the panel looking for some internal driver? Dr. Buckley explained that the drivers for the research are external and not science based. For example, the identification of the susceptible population is a given. The missing element is the public health benefit yielded from the focus on

children's health as opposed to a wide range of other susceptible populations. The panel is looking for some of that science upstream for that identification. Dr. Tilson remarked that "research with a purpose" comes from a number of different sources, most of them external. A large proportion of the drivers for the research program are external. Dr. Buckley stated that a stronger health rationale for the research direction is needed in the materials.

Dr. Symanski stated that the panel's consensus view was that this group is doing the right research, but a complete justification for the nature of the research is missing. A complete description of the scientific basis supporting the decision to focus on children is needed. Dr. Landolph added that this comment does not apply to LTG 1.

Dr. Jayjock reiterated that the research for LTG 2 is correct in the context of risk assessment. The advice is to broaden the program to cover other environmental chemicals.

After final comments and expressions of appreciation from the panel members, Dr. Reiter thanked the panel for its work and praised the efforts of ORD staff in creating a sound and productive program in human health research.

Adjournment

The meeting adjourned at 11:40 a.m.

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Appendix

B • O • S • C

U.S. EPA BOARD OF SCIENTIFIC COUNSELORS
Human Health Subcommittee Meeting

AGENDA
February 28 - March 2, 2005

Environmental Protection Agency
Room C-111A/B/C
109 T.W. Alexander Drive
Research Triangle Park, NC 27711

Monday, February 28, 2005

8:00-8:30 a.m.	Registration	
8:30-8:40 a.m.	Welcome and Opening Remarks	Dr. James Klaunig Chair, Human Health (HH) Subcommittee Dr. James Clark, Vice-Chair, HH Subcommittee
8:40-8:45 a.m.	DFO Welcome and Charge - Administrative Procedures and FACA Rules - Objective of This Subcommittee and Charge	Virginia Houk (EPA) DFO, HH Subcommittee
8:45-8:50 a.m.	ORD's Welcome	Dr. William Farland (EPA) Acting DAA–Science, ORD
8:50-9:10 a.m.	Introduction to the Review of ORD's HH Research Program	Dr. Lawrence Reiter (EPA) Director, NHEERL
9:10-9:45 a.m.	Overview of the HH Research Program	Dr. Larry Cupitt (EPA) ORD/NERL

HH Research Program LTG 1: Use of Mechanistic Data in Risk Assessment

9:45-10:15 a.m.	LTG 1: Overview - Use of Mechanistic Data in Risk Assessment	Dr. Julian Preston (EPA) ORD/NHEERL
10:15-10:30 a.m.	Break	
10:30 a.m.-12:00 noon	LTG 1: Poster Session (Atrium)	HH Subcommittee

12:00-12:30 p.m.	LTG 1: Discussion	HH Subcommittee
12:30-1:30 p.m.	Working Lunch	HH Subcommittee

HH Research Program LTG 2: Aggregate/Cumulative Risk

1:30-2:00 p.m.	LTG 2: Overview - Aggregate/ Cumulative Risk	Dr. Jerry Blancato (EPA) ORD/NERL
2:00-3:30 p.m.	LTG 2: Poster Session (Atrium)	HH Subcommittee
3:30-4:00 p.m.	LTG 2: Discussion	HH Subcommittee
4:00-4:15 p.m.	Break	
4:15-5:30 p.m.	Discussion and Work Session - Work on Draft Report	HH Subcommittee
5:30 p.m.	Adjourn	

Tuesday, March 1, 2005

8:30-8:40 a.m.	Review of Yesterday's Activities Overview of Today's Agenda	Dr. James Klaunig Chair, HH Subcommittee

HH Research Program LTG 3: Susceptible Subpopulations

8:40-9:10 a.m.	LTG 3: Overview - Susceptible Subpopulations	Dr. John Vandenberg (EPA) ORD/NCEA
9:10-11:15 a.m.	LTG 3: Poster Session (Atrium)	HH Subcommittee
11:15-11:30 a.m.	Break	
11:30 a.m.-12:15 p.m.	LTG 3: Discussion	HH Subcommittee
12:15-1:30 p.m.	Working Lunch	HH Subcommittee

HH Research Program LTG 4: Evaluating Public Health Outcomes

1:30-1:50 p.m.	LTG 4: Overview - Evaluating Public Health Outcomes	Dr. Hal Zenick (EPA) ORD/NHEERL
1:50-2:10 p.m.	LTG 4: Discussion	HH Subcommittee
2:10-2:25 p.m.	Public Comments	
2:25-2:40 p.m.	Break	
2:40-3:10 p.m.	Relevance of HH Research Program EPA Extramural Perspective	Dr. George Lambert Robert Wood Johnson Medical School
3:10-5:30 p.m.	Discussion and Work Session - Work on Draft Report	HH Subcommittee
5:30 p.m.	Adjourn	

Wednesday, March 2, 2005

8:30-8:40 a.m.	Review of Prior Day's Activities Overview of Today's Agenda	Dr. James Klaunig Chair, HH Subcommittee
8:40-9:00 a.m.	Relevance of HH Research Program EPA Program Office Perspective	Dr. Randy Perfetti (EPA) Office of Science Coordination and Policy
9:00-9:20 a.m.	Relevance of HH Research Program EPA Regional Perspective	Dr. David Macarus (EPA) Region 5
9:20-9:40 a.m.	Relevance of HH Research Program EPA Office of Children's Health Protection (OCHP) Perspective	Dr. Michael Firestone (EPA) OCHP
9:40-9:55 a.m.	Break	
9:55-11:00 a.m.	Discussion and Work Session - Develop Oral Report	HH Subcommittee
11:00 a.m.-12:00 noon	Oral Report on Charge Questions	HH Subcommittee
12:00 noon	Adjourn	